Please amend the application as follows:

In the specification:

Replace the present application title, at the top of page 1, with the new title set forth below.

B1 PHOSPHINYLOXY, OXIME AND CARBOXYLIC ACID DERIVATIVES WHICH ARE USEFUL AS CARBOXYPEPTIDASE U INHIBITORS

Replace the paragraph on page 1, lines 16-23 with the new paragraph below.

B2 Fibrinolysis is the result of a series of enzymatic reactions resulting in the degradation of fibrin by plasmin. The activation of plasminogen is the central process in fibrinolysis. The cleavage of plasminogen to produce plasmin is accomplished by the plasminogen activators, tissue-type plasminogen activator (t-PA) or urokinase-type plasminogen activator (u-PA). Initial plasmin degradation of fibrin generates carboxy-terminal lysine residues that serves as high-affinity binding sites for plasminogen. Since plasminogen bound to fibrin is much more readily activated to plasmin than free plasminogen, this mechanism provides a positive feedback regulation of fibrinolysis.

Replace the paragraph on page 2, lines 1-3 with the new paragraph below.

B3 By inhibiting the loss of lysine binding sites for plasminogen and thus ~~increase~~ increasing the rate of plasmin formation, effective inhibitors of carboxypeptidase U would be expected to facilitate fibrinolysis.

Replace the paragraph on page 2, lines 16-18 with the new paragraph below.

B4 It has surprisingly been found that compounds of the Formula I are particularly effective as inhibitors of carboxypeptidase U and thereby useful as medicaments for the treatment or ~~profylaxis~~ prophylaxis of conditions wherein inhibition of carboxypeptidase U is beneficial.

Replace the paragraph on page 12, lines 6-10 with the new paragraph below.

B5 The term "cycloalkyl" denotes a saturated or unsaturated, substituted or unsubstituted, non-aromatic ring composed of 3, 4, 5, 6 or 7 carbon atoms, and includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, ~~cycloheptyl~~

B5 Cont

cycloheptyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclopentadienyl, cyclohexadienyl and cycloheptadienyl groups.

Replace the paragraph on page 12, lines 14-16 with the new paragraph below.

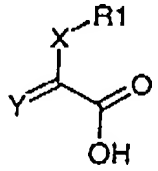
B6

The term "aryl" denotes a substituted or unsubstituted C_6-C_{14} aromatic hydrocarbon and includes, but is not limited to, phenyl, naphthyl, indenyl, ~~antracenyl, fenantrenyl~~ anthracenyl, phenanthrenyl, and fluorenyl.

Replace step c) on page 15, lines 3-6, with the new step below.

B7

c) Compounds of the general Formula V can thereafter be converted to compounds of the general Formula VI,



(VI)

by treatment with formaldehyde in the presence of a suitable base, such as Et_2NH, under standard conditions.

Replace the paragraph on page 16, lines 1-4 with the new paragraph below.

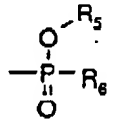
38 Compounds of the general Formula VIII can thereafter be reacted with an appropriate aldehyde CHO(Z), wherein Z is as defined for Formula I, in the presence of a suitable base, such as KOtBu, LDA or NaH, under standard conditions to give ~~to give~~ a compound of the general Formula VI.

Replace step d) on page 16, lines 6-14, with the new step below.

39 d) Compounds of the general Formula VI can be further reacted with compounds of the general Formula IX

$$R_6PO_2H_2 \qquad (IX)$$

wherein R_6 is as defined for Formula I, in the ~~presnee~~ presence of a suitable reagent, such as BSA or HMDS, under standard conditions to give compounds of the general Formula I, wherein R_1, R_5, R_6 and Z are as defined above, R_2 is H, R_3 is $COOR_5$,

R_4 represents a  -group,

X is $C(Z)_2$, and Y is $C(Z)_2$.

Replace the paragraph on page 18, lines 8-10 with the new paragraph below.

B10 Process C for manufacture of compounds with the general Formula I, wherein R_1 and R_2 are as defined above, ~~and~~ X is $C(Z)_2$, ~~and~~ Y is $C(Z)_2$ or a single bond, and R_3 and R_4 are $COOR_5$, comprises the following steps,

Replace step b) on page 19, lines 4-7, with the new step below.

B11 b) hydrolysing a compound of the general Formula XV, for example by treatmcnt with aqueous NaOH or aqueous TFA under standard conditions to give compounds of the general Formula I, wherein R_1 and R_2 are as defined above, ~~and~~ X is $C(Z)_2$, ~~and~~ Y is $C(Z)_2$ or a single bond, and R_3 and R_4 are COOH.

Replace the paragraph on page 23, lines 14-23 with the new paragraph below.

B12 It is known that hypercoagulabililty may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned ir.clude protein

C resistance and inherited or aquired deficiencies in antithrombin III, protein C, protein S and heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulatory and septic shock, circulating antiphospholipid antibodies, ~~homocysteinami~~ homocysteinemia, heparin-induced thrombocytopenia and defects in fibrinolysis. The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions. The compounds of the invention are further indicated in the treatment of conditions where there is an undesirable excess of proCPU/CPU.

B12 cont

Replace step (b) on page 41, lines 16-21, with the new step below.

B13

(b) 2-(6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid

To a solution of *N*-Benzyl-*N*-benzyloxy-2-(6-tert-butoxycarbonylamino-pyridin-3-ylmethyl)-succinamic acid tert-butyl ester (1.0 g, 1.7 mmol) in methylene chloride (10 mL) was added TFA (4 mL) at 0°C. The reaction mixture was stirred for 4 hs and then concentrated under reduced pressure to give crude 2-

B13 (6-Amino-pyridin-3-ylmethyl)-*N*-benzyl-*N*-benzyloxy-succinamic acid as the TFA salt (0.9 g, 100%).

Replace step (c) on page 42, lines 26-32, with the new step below.

B14 (c) 2-(6-Amino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid

To a mixture of 2-(6-*tert*-butoxycarbonylamino-pyridin-3-ylmethyl)-3-[hydroxy-(3-phenyl-propyl)-phosphinoyl]-propionic acid (0.170 g, 0.367 mmol) in ethylacetate (3 mL) at 4°C was slowly added ethylacetate (4 mL. saturated with HCl(g)). The mixture was then stirred for 22 h. Concentration under reduced pressure gave the title compound (0.124 g, 93%) as the hydrochloride salt.

Replace step (b) running from page 43, line 25 through page 44, line 5, with the new step below.

B15 (b) 2-[(1-Benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]3-(6-tert-butoxycarbonylamino-5-methyl-pyridin-3-yl-propionic acid

1 M LiOH (2 mL) was added dropwise to a solution of 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-

phosphinoylmethyl]-3-(6-bis(tert-butoxycarbonyl)amino-5-methyl-pyridin-3-yl)-propionic acid ethyl ester (100 mg, 0.145 mmol) in acetonitrile (2 mL). The mixture was stirred overnight and concentrated under reduced pressure. The mixture was purified by column chromatography (isopropanol/concentrated aqueous NH_3/water, 4:2:1) to give ~~unpure~~ impure product. The ~~unpure~~ impure product was stirred with MeOH, filtered and concentrated under reduced pressure. The crude product was stirred with EtOH, filtered and concentrated under reduced pressure. The crude product was stirred with ethylacetate/ethanol, filtered and concentrated under reduced pressure to give 2-[(1-benzyloxycarbonylamino-2-methyl-propyl)-hydroxy-phosphinoylmethyl]-3-(6-tert-butoxycarbonylamino-5-methyl-pyridin-3-yl)-propionic acid (52 mg, 63.8%).

B15

Replace the definition on page 48, line 28, with the new definition below.

B16

TEA = ~~trietylamine~~ triethylamine